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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,207	02/13/2006	Mitsuo Oshimura	081356-0239	1647

22428 7590 11/25/2008

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EXAMINER	
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ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
11/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,207	OSHIMURA ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *1-17,23-25,29-32 and 34-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-22,26-28,33 and 37-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :April 4, 2005, May 8, 2006 and August 29, 2006.

Effective October 1, 2008, the Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Kevin K. Hill, Art Unit 1633 whose contact information is provided at the end of this Action.

Detailed Action

Election/Restrictions

Applicant's response to the Requirement for Restriction, filed on June 27, 2008 is acknowledged. Applicant has elected the invention of Group III, claim(s) 18-23, 26-28, 33 and 37-48, drawn to a method of making a human artificial chromosome vector comprising obtaining cells that retain human chromosome 21 and deleting a distal region of the long or short arm of the human chromosome 21.

Within Group III, Applicant has elected the deletion site species "AL163204".

Election of Applicant's invention(s) was made with traverse in that the Examiner has shown no undue burden associated with searching all claims together.

Applicants' arguments have been fully considered but are not found persuasive. MPEP §803 states that "If the search and examination of all the claims in an application can be made without serious burden, the Examiner must examine them on the merits, even though they include claims to independent or distinct inventions."

In the instant case a serious burden exists since each limitation, directed to human artificial chromosomes comprising distinctly different chromosomal regions, e.g. Chr. 14 or Chr. 21, as well as the plurality of claimed deletion sites (see Groups II and IV, for example), requires a separate, divergent, and non co-extensive search and examination of the patent and non-patent literature. For instance, a search and consideration of the prior art as it relates to Chromosome 14 would not be adequate to uncover prior art related to Chromosome 21. Similarly, prior art regarding deletion site K12T would not be adequate to uncover prior art regarding AL163204.

Further, a search and examination of all the claims directed to both embodiments involves different considerations of novelty, obviousness, written description, and enablement for each

claim. In view of these requirements, it is the Examiner's position that searching and examining all of the claims in the same application presents a serious burden on the Examiner for the reasons given above and in the previous Restriction Requirement.

The requirement is still deemed proper and is therefore made FINAL.

1. **Claims 18-22, 26-28, 33 and 37-46 are objected to because of the following informalities**: the claims are drawn to non-elected subject matter, specifically "human chromosome 14", and claims dependent therefrom, e.g. claims 26-28 and 33. It would be remedial to draft the claims in independent form.

This application contains claims drawn to an invention nonelected with traverse in the reply filed on June 27, 2008. A complete reply to the non-final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP §821.01.

Appropriate correction is required.

Amendments

In the reply filed June 27, 2008, Applicant has cancelled Claims 47-48.

Claims 1-17, 23-25, 29-32 and 34-36 are pending but withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Claims 18-22, 26-28, 33 and 37-46 are under consideration.

Priority

This application is a 371 of PCT/JP03/12734, filed on October 3, 2003. Acknowledgment is made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). Certified copies, but not English translations, of PCT/JP03/12734, filed on October 3, 2003 and JP2002-202853 filed on October 4, 2002 have been filed with the instant application.

Accordingly, the effective priority date of the instant application is granted as October 4, 2002.

Information Disclosure Statement

Applicant has filed Information Disclosure Statements on April 4, 2005, May 8, 2006 and August 29, 2006 that have been considered.

The signed and initialed PTO Forms 1449 are mailed with this action.

Specification

2. **The disclosure is objected to** because it contains an embedded hyperlink and/or other form of browser-executable code (pg 17, ¶8; pg 22, ¶1; pg 23; pg 31; pg 47; pg 52). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP §608.01.

Claim Objections

3. **Claims 22, 26-28 and 33 are objected to under 37 CFR 1.75(c)** as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. See MPEP § 608.01(n). In the interest of compact prosecution, the Examiner interprets claim 22 to be dependent upon claim 21, claim 28 to be dependent upon claim 27, claim 27 to be dependent upon claim 26, and claims 26 and 33 to be dependent upon claim 18.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

4. **Claims 19-20 are rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The term "high…efficiency" in claims 19-20 is a relative term which renders the claim indefinite. The term "high…efficiency" is not defined by the claim, the

specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bounds of what Applicants consider "high…efficiency" is indefinite because the artisan's determination of "high…efficiency" is subjective, dependent upon an arbitrary reference recombination rate.

Appropriate correction is required.

5. **Claim 20 is rejected under 35 U.S.C. 112, second paragraph**, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claim 20 is vague and indefinite in that the metes and bounds of the term "derived from" is unclear. It is unclear the nature and number of steps required to obtain a "derivative" of the chicken DT40 cells possessing high homologous recombination efficiency. The term implies a number of different steps that results in a change in the functional characteristics of the cell that it is "derived from". For example, it is unclear if an unrecited structural feature and/or method step is required to render a DT40 cell having low homologous recombination efficiency to become a cell having high homologous recombination efficiency. Thus, the essential feature necessary to achieve "high...efficiency" is not recited in the claim.

The Examiner notes that the instant specification discloses that DT40 cells inherently possess "high homologous recombination efficiency" (pg 20, ¶2), and thus it would be remedial to amend the claim language to delete the term "derived from", unless Applicant has further modified the DT40 cells as part of the instant inventive method to achieve "high homologous recombination efficiency", in which case, such a feature should be claimed.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. **Claims 41 and 46 are rejected under 35 U.S.C. 112, first paragraph**, because the specification, while being enabling for methods for producing a mouse embryonic stem (ES) cell comprising a modified foreign chromosome or fragments thereof, does not reasonably provide enablement for methods for producing embryonic stem (ES) cells from an enormous genus of biologically distinct organisms comprising modified foreign chromosomes or fragments thereof.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

The claims are broad for encompassing about 1,000,000 species of animals (waynesword.palomar.edu/trfeb98.htm, last visited November 26, 2007). Mammalian subjects reasonably encompasses some 5,500 species (including humans), distributed in about 1,200 genera, 152 families and up to 46 orders (en.wikipedia.org/wiki/Mammal, last visited March 21, 2007), wherein the art teaches that there are approximately 4,000 rodent species, divided into

three major groups or sub-orders, Sciuromorpha, Myomorpha and Hystricomorpha, and more than 30 families. The diversity of instantly claimed rodent genus reasonably encompasses, for example, squirrels, chipmunks, beavers, woodchucks, prairie dogs, hamsters, lemmings, voles, porcupines, capybaras, agoutis, chinchilla, as well as many species whose common names include the term "rat" (columbia.thefreedictionary.com/rodent).

The claimed invention is directed to methods for producing a mouse embryonic stem (ES) cell comprising a modified foreign chromosome or a fragment thereof, comprising preparing a microcell comprising a foreign chromosome or a fragment thereof, and transferring said foreign chromosome or a fragment thereof into a cell with high homologous recombination efficiency through its fusion with said microcell, in said cell with high homologous recombination efficiency, inserting a targeting vector by homologous recombination into a desired site of said foreign chromosome or fragment thereof and a desired site of a chromosome derived from said cell with high homologous recombination efficiency, thereby marking the desired site; and causing the deletion and/or translocation to occur at the marked site of the foreign chromosome or fragment thereof.

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

The inventive concept in the instant application is the use of mouse embryonic stem (ES) cells (pg 18, lines 4-5; pg 128, Example 24), wherein such ES cells may then be used to generate chimeric mice to establish germline transmission of the telomere-truncated human chromosome fragment (pg 27, ¶3).

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

The claimed invention is directed to embryonic stem (ES) cells that comprise modified foreign chromosomes or fragments thereof. However, the state of the art is such that ES cell technology is generally limited to the mouse system at present, and that only "putative" ES cells exist for other species (see Moreadith et al, J. Mol. Med., 1997, p. 214, Summary). Note that "putative" ES cells lack a demonstration of the cell to give rise to germline tissue or the whole animal, a demonstration which is an art-recognized property of ES cells. Moreadith et al supports

this observation as they discuss the historical perspective of mouse ES cells as follows: "The stage was set-one could grow normal, diploid ES cells in culture for multiple passages without loss of the ability to contribute to normal development. Furthermore, the cells contributed to the development of gametes at a high frequency (germline competence) and the haploid genomes of these cells were transmitted to the next generation. Thus, the introduction of mutations in these cells offered the possibility of producing mice with a predetermined genotype."

Such a demonstration has not been provided by the specification or the prior or post-filing art with regard to the generation of any species of animal ES cells, other than the mouse, which can give rise to the germline tissue of a developing animal. In addition, prior to the time of filing, Mullins et al (Journal of Clinical Investigation, 1996) report that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." (pg 1558, col. 2, ¶1). As the claims are drawn to methods involving the manipulation of animal embryonic stem (ES), the state of the art supports that only mouse ES cells were available.

This is further supported by Pera et al (Journal of Cell Science 113:5-10, 2000) who present the generic criteria for pluripotent ES or EG cells and state that, "Thus far, only mouse EG or ES cells meet these generic criteria. Primate ES cells meet the first three of the four criteria, but not the last. Numerous other candidate mammalian ES cells have been described over the years in domestic and laboratory species, but only in the mouse have all criteria been met rigorously." (see pg 6, col. 2, last ¶)

The physiological art is recognized as unpredictable. (MPEP §2164.03) In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved. The art teaches that the properties of embryonic stem cells are highly species specific and that processes developed using a mouse ES cell cannot be generically applied to all ES cells. In particular, the art recognizes that ES cells isolated from different

species exhibit significantly different properties. Wheeler (US Patent No. 5,942,435) describes many problems encountered in extending successes obtained with mouse ES cells to other mammalian species. For example, Wheeler teaches that attempts to establish useful stem cells from pigs and sheep produced disappointing results (col. 2, ¶3; col. 3, ¶5); and teaches that a problem "in extrapolating from mice to ungulates, such as swine, is that exactly analogous stages do not exist in the embryos of mice and ungulates..." (col. 4, ¶2). Thus, establishing ES cell lines from other species of mammals or animals having properties that are analogous to the mouse ES cells used in the methods of the instant application is highly unpredictable. It is noted that the unpredictability of a particular area may alone provide reasonbale doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991).

The Quantity of Any Necessary Experimentation to Make or Use the Invention

Accordingly, in view of the state of the art of ES cells, and the lack of guidance or teachings provided by the specification for the availability of ES cells from species other than mouse, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

In conclusion, the specification fails to provide any guidance as to how an artisan would have dealt with the art-recognized limitations of the claimed method commensurate with the scope of the claimed invention and therefore, limiting the claimed invention to a method comprising the use of a mouse embryonic stem (ES) cell comprising a modified foreign chromosome or fragments thereof, is proper.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. **Claims 18-21, 26-27, 33 and 37-46 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Kuroiwa et al (NAR 26(14):3447-3448, 1998; *of record in IDS) in view of Kuroiwa et al (Nature Biotechnol. 18:1086-1090, 2000; *of record in IDS) and Tomizuka et al (Nature Genetics 16:133-143, 1997; *of record in specification).

Determining the scope and contents of the prior art.

Kuroiwa et al teach a method for producing a human artificial chromosome vector and a method of introducing foreign DNA into a recipient cell, the methods comprising the step of obtaining donor cells that retain human chromosome 22, deleting a distal region of the long arm and/or a distal region of the short arm of the human chromosome 22, wherein the deletion step is by substitution with an artificial telomere sequence, wherein the cells that retain human

chromosome 22 are chicken DT40 cells that have a high homologous recombination rate (pg 3447, Figure 1).

Kuroiwa et al do not teach the step of inserting a recognition site for a site-specific recombination enzyme into a proximal region of the long arm and/or a proximal region of the short arm of the human chromosome. However, at the time of the invention, Kuroiwa et al (2000) taught a method for producing a human artificial chromosome vector, the method comprising the **combination of** a chromosome comprising site-specific, Cre/loxP-mediated, homologous recombination and telomere-directed chromosome truncation in homologous recombination-proficient chicken DT40 cells, and the step of inserting foreign DNA into the human chromosome in the presence of a site-specific recombination enzyme. The site-specific recombination recognition site, loxP, was integrated into a locus of the human chromosome. Kuroiwa et al teach the step of preparing microcells from the donor cells that retain the human chromosome and fusing the microcells comprising a human chromosomal vector to a recipient cell that is a mouse embryonic stem cell, wherein those of ordinary skill in the art recognize ES cells to reasonably embrace mesenchymal and tissue stem/precursor cells given their developmental totipotentcy, the step of selecting cells expressing the foreign DNA among the fused recipient cells, and the step of confirming the introduction of the foreign DNA into the fused recipient cells, e.g. by FISH analysis. Kuroiwa et al suggest that various human chromosomal regions defined by loxP-integration and telomere-truncation sites can be cloned by this method. The cloning capacity is at least 10 Mb greater than in conventional cloning methods (pg 1086; pg 1087, col. 1, Figure 1; pg 1088, Figure 2).

Kuroiwa et al (1998, 2000) do not teach the human chromosome to be chromosome 21. However, at the time of the invention, Tomizuka et al taught a method of producing a human artificial chromosome vector, a method of introducing foreign DNA into a recipient cell, and producing a cell that expresses foreign DNA, the methods comprising the use of a library of human-mouse A9 monochromosomal hybrids that retain human chromosomes, wherein each human chromosome is randomly tagged with a selectable marker suitable for use in mouse ES cells. Tomizuka et al teach the step of obtaining cells that retain human chromosome 14 or 22,

the step of preparing microcells from the donor cells that retain the human chromosome and fusing the microcells comprising a human chromosomal vector to a recipient cell that is a mouse embryonic stem cell, wherein those of ordinary skill in the art recognize ES cells to reasonably embrace mesenchymal and tissue stem/precursor cells given their developmental totipotentcy, the step of selecting cells expressing the foreign DNA, e.g. G418 resistance, among the fused recipient cells, and the step of confirming the introduction of the foreign DNA into the fused recipient cells, e.g. by FISH analysis (pg 133, col. 2; pg 134, col. 1, Figures 1 and 2). Tomizuka et al teach that using the Cre-loxP system, replacing a specific mouse chromosomal region with the corresponding human chromosomal fragment will be possible (pg 140, col. 2, ¶2). Tomizuka et al teach that efforts to repeat the method using human Chromosome 21 are underway to investigate various aspects of Down's syndrome (pg 140, col. 1, ¶2).

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in molecular biology and the creation of transgenic cells comprising artificial/recombinant human chromosomes. Therefore, the level of ordinary skill in this art is high. The technology to shorten a chromosome by introducing a cloned telomere sequence by homologous recombination (telomere truncation) has been practiced in the art since 1992 (Specification, pg 21).

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to combine the instantly recited method steps into a single method for producing a human artificial chromosome vector, introducing foreign DNA into a recipient cell, and producing a cell that expresses foreign DNA with a reasonable chance of success because all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with

no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. It is well known that it is *prima facie* obvious to combine two or more ingredients each of which is taught by the prior art to be useful for the same purpose in order to form a third composition which is useful for the same purpose (as well as to use such a composition for that purpose). The idea for combining them flows logically from their having been used individually in the prior art, and from them being recognized in the prior art as useful for the same purpose. This rejection is based on the well established proposition of patent law that no invention resides in combining old ingredients of known properties where the results obtained thereby are no more than the additive effect of the ingredients. *In re Kerkhoven*, 626 F.2d 846, 850, 205 U.S.P.Q. 1069 (CCpA 1980), *In re Sussman*, 1943 C.D. 518; *In re Pinten*, 459 F.2d 1053, 173 USPQ 801 (CCPA 1972); *In re Susi*, 58 CCPA 1074, 1079-80; 440 F.2d 442, 445; 169 USPQ 423,426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21; 279 F.2d 274, 276-277; 126 USPQ 186, 188 (1960). In the instant case, all such method steps were practiced in smaller combinations by the ordinary artisan in methods for producing a human artificial chromosome vector, introducing foreign DNA into a recipient cell, and producing a cell that expresses foreign DNA. An artisan would be motivated to combine the instantly recited method steps into a single method for producing a human artificial chromosome vector, introducing foreign DNA into a recipient cell, and producing a cell that expresses foreign DNA because Kuroiwa et al (2000) teach the successful combination of site-specific, homologous recombination and telomere-directed chromosome truncation in homologous recombination-proficient chicken DT40 cells.

It also would have been obvious to one of ordinary skill in the art to substitute a first human chromosome as taught by Kuroiwa et al (1998, 2000) and/or Tomizuka et al with a second human chromosome that is chromosome 21 with a reasonable chance of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945) "Reading a list and selecting a known compound to meet known requirements is no more ingenious than selecting the last piece to put in the last opening in a jig-saw puzzle."

325 U.S. at 335, 65 USPQ at 301.)". When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. In the instant case, those of ordinary skill in the art recognized that the human genome comprises a finite set of chromosomes, and Tomizuka et al teach that construction of human artificial chromosome vectors comprising human chromosome 21 is of biological interest, e.g. the study of Down's Syndrome.

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

8. **Claims 22 and 28 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Kuroiwa et al (NAR 26(14):3447-3448, 1998; *of record in IDS) in view of Kuroiwa et al (Nature Biotechnol. 18:1086-1090, 2000; *of record in IDS) and Tomizuka et al (Nature Genetics 16:133-143, 1997; *of record in specification), as applied to claims 18-21, 26-27, 33 and 37-46 above, and in further view of Hattori et al (Nature 405(6784):311-319, 2000).

Determining the scope and contents of the prior art.

Neither Kuroiwa et al (1998, 2000) nor Tomizuka et al teach the wherein in step (b) the distal region of the long arm of human chromosome 21 is deleted at AL163204 (c22), and wherein the recognition site for the site- specific recombination enzyme is inserted into AL163203 in the proximal region of the long arm of human chromosome 21 (c28). However, at the time of the invention, Hattori et al taught the nucleotide sequence and annotation of human chromosome 21, achieving 99.7% coverage of 21q, within which AL163203 and AL163204 reside.

Ascertaining the differences between the prior art and the claims at issue, and Resolving the level of ordinary skill in the pertinent art.

People of the ordinary skill in the art will be highly educated individuals such as medical doctors, scientists, or engineers possessing advanced degrees, including M.D.'s and Ph.D.'s. Thus, these people most likely will be knowledgeable and well-read in the relevant literature and have the practical experience in molecular biology and the creation of transgenic cells

comprising artificial/recombinant human chromosomes. Therefore, the level of ordinary skill in this art is high.

The nucleotide sequence (Accession No. AL163204) of the long-arm distal region of human chromosome 21 was obtained from the GenBank database (Specification, pg 50, ¶1).

Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one of ordinary skill in the art to try substituting the insertion site of the recognition site for the site-specific recombination into AL163203 for the insertion site of Kuroiwa et al (1998, 2000) in view of Tomizuka et al and the deletion of the region distal to AL163204 for the telomere truncations as per the teachings of Kuroiwa et al (1998, 2000) in view of Tomizuka et al with a reasonable chance of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention, and "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipate success, it is likely that product not of innovation but of ordinary skill and common sense." M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945) "Reading a list and selecting a known compound to meet known requirements is no more ingenious than selecting the last piece to put in the last opening in a jig-saw puzzle." 325 U.S. at 335, 65 USPQ at 301.)". When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. In the instant case, the nucleotide sequence of human chromosome 21 was known in the prior art, and thus the ordinary artisan had access to those specific sequences necessary to design a specific telomere-truncation chromosome 21 vector comprising a specific insertion site of the recognition site for the site-specific recombination and a specific deletion of the region distal of the long and/or short arm of human chromosome 21 that retains one or more desired human chromosome 21 genes, and has removed one or more undesired human chromosome 21 genes so as to facilitate the

study of the artisan's gene of interest (Hattori et al, pg 317-318, Medical Implications, Monogenic disorders, Complex Phenotypes, Neoplasias).

Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Conclusion

9. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to KEVIN K. HILL whose telephone number is (571)272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Kevin K. Hill, Ph.D./

Examiner, Art Unit 1633

/Q. JANICE LI, M.D./

Primary Examiner, Art Unit 1633